HOSPIMAX
Maximising Life

Hoslina™-M 2.5 mg/ 500 mg

Linagliptin 2.5 mg + Metformin 500 mg Tablets

Effective, Safe, Convenient

Product Description:

Each film coated tablet contains Linagliptin 2.5mg and Metformin 500mg.

Description:

Linagliptin is an oral inhibitor of dipeptidyl peptidase-4 (DPP-4). It is the first agent of its class to be eliminated predominantly via a nonrenal route.

Metformin is an antihyperglycemic agent of the *biguanide* class, used for the management of type II diabetes). Currently, metformin is the first drug of choice for the management of type II diabetes and is prescribed to at least 120 million people worldwide

Indications:

Hoslina-M is indicated in adults with type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control.

Dosage:

The recommended dose of Hoslina-M is twice daily.

Mode of Action:

Hoslina-M Tablet is a combination of two antidiabetic medications.

Linagliptin is a potent, reversible, and selective inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4) which is involved in the inactivation of the incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels.

Metformin decreases blood glucose levels by decreasing hepatic glucose production (gluconeogenesis), decreasing the intestinal absorption of glucose, and increasing insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics:

Linagliptin:

Absorption:
The absolute bioavailability of linagliptin is approximately 30%. Co-administration of a high-fat meal with linagliptin prolonged the time to reach Cmax by 2 hours and lowered Cmax by

15% but no influence on AUC 0-72h was observed. No clinically relevant effect of Cmax and Tmax changes is expected; therefore linagliptin may be administered with or without food.

The absolute bioavailability of a metformin 500 mg tablet administered in the fasting state is about 50%-60%. Single-dose clinical studies using oral doses of metformin 500 to 1500 mg and 850 to 2550 mg show that there is a lack of dose proportionality with an increase in metformin dose, attributed to decreased absorption rather than changes in elimination

Distribution:
As a result of tissue binding, the mean apparent volume of distribution at steady-state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1,110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/l to 75-89% at ≥30 nmol/l, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70-80% of linagliptin was bound to other plasma proteins than DPP-4, hence 30-20% were unbound in plasma.

The apparent volume of distribution (V/F) of metformin after one oral dose of metformin 850 mg averaged at 654 ± 358 L

Biotransformation:
Following linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3% of linagliptin at steady-state was detected which was found to be pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.
Intravenous studies using a single dose of metformin in normal subjects show that metformin is excreted as unchanged drug in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion

Elimination: Following administration of an oral linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady-state was approximately 70 ml/min.

Metformin is substantially excreted by the kidney. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Method of administration: Hoslina-M should be taken twice daily with meals to reduce the gastrointestinal adverse reactions associated with metformin.

All patients should continue their diet with an adequate distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet. If a dose is missed, it should be taken as soon as the patient remembers. However, a double dose should not be taken at the same time. In that case, the missed dose should be skipped.

Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in Description. Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis).

Diabetic pre-coma.
Severe renal failure (GFR <30 ml/min).
Acute conditions with the potential to alter renal function such as: dehydration, severe infection, shock.
Disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic disease) such as: decompensated heart failure, respiratory failure, recent myocardial infarction, shock.
Hepatic impairment, acute alcohol intoxication, alcoholism.

Drug Interaction:

Linagliptin

Sulphonylureas: co-administration of multiple oral doses of 5 mg linagliptin and a single oral dose of 1.75 mg glibenclamide (glyburide) resulted in clinically not relevant reduction of 14% of both AUC and Cmax of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g., glipizide, tolbutamide, and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Digoxin: co-administration of multiple daily doses of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy volunteers. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport in vivo.

Warfarin: multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, administered in a single dose.

Simvastatin: multiple daily doses of linagliptin had a minimal effect on the steady-state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of a supratherapeutic dose of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma Cmax by 10%.

Metformin: *Combination requiring precautions for use:* Glucocorticoids (given by systemic and local routes), beta-2-agonists, and diuretics have intrinsic hyperglycaemic activity. The patient should be informed and more frequent blood glucose monitoring performed,

especially at the beginning of treatment with such medicinal products. If necessary, the dose of the anti-hyperglycaemic medicinal product should be adjusted during therapy with the other medicinal product and on its discontinuation.
Some medicinal products can adversely affect renal function which may increase the risk of lactic acidosis, e.g. NSAIDs, including selective cyclo-oxygenase (COX) II inhibitors, ACE inhibitors, angiotensin II receptor antagonists and diuretics, especially loop diuretics. When starting or using such products in combination with metformin, close monitoring of renal function is necessary.
Organic cation transporters (OCT): Metformin is a substrate of both transporters OCT1 and OCT2. Co-administration of metformin with: Inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
Inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase in metformin plasma concentration.
Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.
Caution is therefore advised, especially in patients with renal impairment, when these drugs are coadministered with metformin, as metformin plasma concentration may increase. If needed, dose adjustment of metformin may be considered as OCT inhibitors/inducers may alter the efficacy of metformin.

Use in specific population

- **Renal impairment** –GFR should be assessed before treatment initiation and regularly thereafter. Metformin is contraindicated in patients with GFR<30 ml/min and should be temporarily discontinued in the presence of conditions that alter renal

- **Elderly (≥ 65 years)** -No dose adjustments are necessary in elderly patients

- **Pregnancy:** The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity
  A limited amount of data suggests that the use of metformin in pregnant women is not associated with an increased risk of congenital malformations. Hoslina-M should not be used during pregnancy. If the patient plans to become pregnant, or if pregnancy occurs, treatment with Hoslina-M should be discontinued and switched to insulin treatment as soon as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

- **Lactation** -Studies in animals have shown excretion of both metformin and linagliptin into milk in lactating rats. Metformin is excreted in human milk in small amounts. It is not known whether linagliptin is excreted into human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Hoslina-M

therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman

Adverse Reactions

The most frequently reported adverse reaction for linagliptin plus metformin was diarrhoea (1.6%) with a comparable rate on metformin plus placebo (2.4%).

Hypoglycaemia:
When linagliptin and metformin were administered in combination with insulin, hypoglycaemia was the most frequently reported adverse event, but occurred at comparable rate when placebo and metformin were combined with insulin (linagliptin plus metformin plus insulin 29.5% and 30.9% in the placebo plus metformin plus insulin group) with a low rate of severe (requiring assistance) episodes (1.5% and 0.9%). *Other adverse reactions:* Gastrointestinal disorders such as, nausea, vomiting, diarrhoea and decreased appetite and abdominal pain occur most frequently during initiation of therapy with Hoslina-M Duo or metformin hydrochloride and resolve spontaneously in most cases